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An Efficient Synthesis of 3,4-Dihydropyrimidin-2-(1*H*)-one Derivatives Promoted by Antimony Trichloride under Thermal and Solvent-free Conditions

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An efficient and simple one-pot approach for the synthesis of 3,4-dihydropyrimidin-2-(1*H*)-one derivatives using antimony trichloride ($SbCl_3$) as a mild catalyst by means of three-component Biginelli reaction between β-keto esters, aldehyde derivatives and urea/thiourea under thermal and solvent-free conditions with excellent yields and short reaction times is reported. This methodology offers several merits such as excellent yields, short reaction times, efficient, eco-friendly, solvent-free conditions, materials available, and simple operational procedure with no column chromatographic separation. The products are characterized by melting points and ^{1}H NMR spectroscopy.

Keywords: Antimony trichloride ($SbCl_3$), 3,4-Dihydropyrimidinone, Multi-component synthesis, Biginelli reaction

INTRODUCTION

The first synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones derivatives was reported by Biginelli [1] in 1893. 3,4-Dihydropyrimidin-2-(1*H*)-ones and their derivatives serve as a major category of heterocyclic compounds. They have received considerable attention because of their wide range of pharmaceutical and biological properties. These compounds have been used as calcium channel blockers, α-1a-antagonists [2], antihypertensive effects [3], anticancer [4], anti HIV agent [5], antibacterial and antifungal [6], antiviral [7], antioxidative [8] and anti-inflammatory [9]. Also some of alkaloids found have dihydropyrimidine unit in their structure, as shown in Fig. 1.

Over the past few decades, multicomponent domino reactions (MCRs) [10-16] have become useful tools for the synthesis of heterocyclic compounds because of a wide range of their properties such as atom-economy, mild and environmentally-friendly, low-cost and one-pot operation.

In recent years, several protocols for the preparation of these compounds have been reported including Lewis and Brønsted acid catalysts such as copper(II) sulfamate [17], bakers' yeast [18], hydrotalcite [19], hexaaquaaluminium(III)tetrafluoroborate [20], TBAB [21], Copper(II) tetrafluoroborate [22], [Btto][*p*-TSA] [23], triethylammonium acetate [24], and *p*-dodecylbenzene-sulfonic acid [25]. Some of the limitations of these methodologies are low yields, toxic organic solvents and catalyst, harsh reaction conditions and expensive materials.

Because of especially pharmaceutical and biological properties 3,4-dihydropyrimidin-2-(1*H*)-one derivatives. This research aims to design a simple and efficient method using multi-component reactions for the synthesis of 3,4-dihydropyrimidin-2-(1*H*)-one derivatives. Herein, we report a simple and mild one-pot approach for the synthesis of 3,4-dihydropyrimidin-2-(1*H*)-one derivatives by using of antimony trichloride ($SbCl_3$) as an efficient and economical catalyst by means of three-component Biginelli reaction between β-keto esters, aldehyde derivatives and urea/thiourea under thermal and solvent-free conditions with excellent yields.

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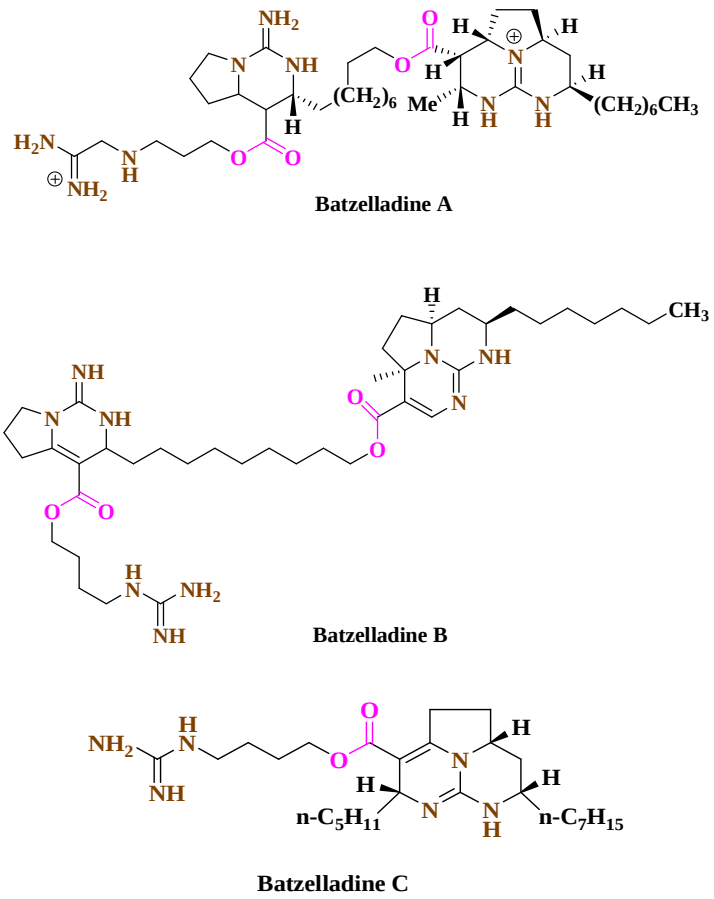


Fig. 1. Batzelladine alkaloids containing the dihydropyrimidine units.

EXPERIMENTAL

Material and Methods

Melting points of all compounds were determined using an Electro thermal 9100 apparatus. Also, nuclear magnetic resonance, ^{1}H NMR spectra were recorded on a Bruker DRX-400 Avance instruments with DMSO-d_6 as the solvent. All reagents and solvents were purchased from Merck, Fluka and Acros chemical companies, and used without further purification.

General Procedure for Preparation of 3,4-Dihydropyrimidin-2-(1*H*)-one Derivatives (4a-n)

A mixture of aldehydes derivatives (1, 1.0 mmol) and urea/thiourea (2, 1.5 mmol), ethyl/methyl acetoacetate (3, 1.0 mmol) under solvent-free conditions was heated for an appropriate time in the presence of $SbCl_3$ (15 mol%) at 70 °C. After completion of the reaction (by thin layer chromatography TLC) the mixture was cooled to rt and cold water was added and the precipitated was separated with filtration and solid was recrystallized from ethanol to afford the pure products (4a-n). Spectral data of the products are represented as below:

5-Ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (4a). M.p.: 200-202 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 1.10 (3H, t, J = 7.2 Hz, $\underline{CH_3}CH_2$), 2.26 (3H, s, CH_3), 3.99 (2H, q, J = 7.2 Hz, CH_2O), 5.15 (1H, s, CHN), 7.26 (3H, d, J = 7.2 Hz, ArH), 7.33 (2H, t, J = 7.2 Hz, ArH), 7.76 and 9.21 (2H, 2s, 2NH).

5-Ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-thione (4b). M.p.: 206-208 °C; ^{1}H NMR

(400 MHz, DMSO-d_6): 1.11 (3H, t, *J* = 7.2 Hz, $\underline{CH_3}CH_2$), 2.31 (3H, s, CH_3), 4.02 (2H, q, *J* = 7.2 Hz, CH_2O), 5.19 (1H, s, CHN), 7.23 (2H, d, *J* = 7.2 Hz, ArH), 7.28 (1H, t, *J* = 7.2 Hz, ArH), 7.36 (2H, t, *J* = 7.2 Hz, ArH), 9.68 and 10.36 (2H, 2s, 2NH).

5-Methoxycarbonyl-6-methyl-4-(2-chloro-phenyl)-3, 4-dihydropyrimidin-2(1H)-one (4c). M.p.: 246-248 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 2.31 (3H, s, CH_3), 3.46 (3H, s, OCH_3), 5.62 (1H, s, CHN), 7.28-7.34 (3H, m, ArH), 7.42 (1H, d, *J* = 7.2 Hz, ArH), 7.72 and 9.36 (2H, 2s, 2NH).

5-Ethoxycarbonyl-6-methyl-4-(2-chloro-phenyl)-3,4-dihydropyrimidin-2(1H)-one (4d). M.p.: 220-222 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 1.00 (3H, t, *J* = 9.2 Hz, $\underline{CH_3}CH_2$), 2.31 (3H, s, CH_3), 4.02 (2H, q, *J* = 9.2 Hz, CH_2O), 5.63 (1H, s, CHN), 7.25-7.34 (3H, m, ArH), 7.41 (1H, d, *J* = 8.8 Hz, ArH), 7.73 and 9.29 (2H, 2s, 2NH).

5-Ethoxycarbonyl-6-methyl-4-(4-methoxy-phenyl)-3, 4-dihydropyrimidin-2(1H)-one (4e). M.p.: 203-205 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 1.11 (3H, t, *J* = 9.6 Hz, $\underline{CH_3}CH_2$), 2.24 (3H, s, CH_3), 3.73 (3H, s, OCH_3), 3.99 (2H, q, *J* = 9.6 Hz, CH_2O), 5.09 (1H, s, CHN), 6.89 (2H, d, *J* = 8.4Hz, ArH), 7.15 (2H, d, *J* = 8.8 Hz, ArH), 7.70 and 9.18 (2H, 2s, 2NH).

5-Ethoxycarbonyl-6-methyl-4-(4-methoxy-phenyl)-3, 4-dihydropyrimidin-2(1H)-thione (4g). M.p.: 150-152 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 1.11 (3H, t, *J* = 9.6 Hz, $\underline{CH_3}CH_2$), 2.29 (3H, s, CH_3), 3.73 (3H, s, OCH_3), 4.00 (2H, q, *J* = 9.6 Hz, CH_2O), 5.14 (1H, s, CHN), 6.68-7.31 (4H, m, ArH), 7.77 and 9.25 (2H, 2s, 2NH).

5-Ethoxycarbonyl-6-methyl-4-(4-fluoro-phenyl)-3,4-dihydropyrimidin-2(1H)-one (4h). M.p.: 172-174 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 1.11 (3H, t, *J* = 9.6 Hz, $\underline{CH_3}CH_2$), 2.25 (3H, s, CH_3), 3.99 (2H, q, *J* = 9.6 Hz, CH_2O), 5.14 (1H, s, CHN), 7.13-7.20 (2H, m, ArH), 7.24-7.29 (2H, m, ArH), 7.78 and 9.25 (2H, 2s, 2NH).

5-Methoxycarbonyl-6-methyl-4-(4-fluoro-phenyl)-3,4-dihydropyrimidin-2(1H)-thione (4i). M.p.: 209-211 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 2.30 (3H, s, CH_3), 3.56 (3H, s, OCH_3), 5.18 (1H, s, CHN), 7.13-7.28 (4H, m, ArH), 9.71 and 10.42 (2H, 2s, 2NH).

5-Ethoxycarbonyl-6-methyl-4-(3-chloro-phenyl)-3,4-dihydropyrimidin-2(1H)-one (4j). M.p.: 192-194 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 1.11 (3H, t, *J* = 9.2 Hz, $\underline{CH_3}CH_2$), 2.26 (3H, s, CH_3), 4.01 (2H, q, *J* = 9.6 Hz, CH_2O), 5.15 (1H, s, CHN), 7.19-7.26 (2H, m, ArH), 7.31-7.41 (2H, m, ArH), 7.83 and 9.30 (2H, 2s, 2NH).

5-Ethoxycarbonyl-6-methyl-4-(4-hydroxy-phenyl)-3,4-dihydropyrimidin-2(1H)-one (4k). M.p.: 232-234 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 1.11 (3H, t, *J* = 9.6 Hz, $\underline{CH_3}CH_2$), 2.50 (3H, s, CH_3), 3.98 (2H, q, *J* = 9.2 Hz, CH_2O), 5.04 (1H, s, CHN), 6.68-7.04 (4H, m, ArH), 7.64 and 9.13 (2H, 2s, 2NH), 9.35 (1H, s, OH).

5-Methoxycarbonyl-6-methyl-4-(4-nitro-phenyl)-3,4-dihydropyrimidin-2(1H)-one (4l). M.p.: 215-217 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 2.28 (3H, s, CH_3), 3.55 (3H, s, OCH_3), 5.28 (1H, s, CHN), 7.52 (2H, d, *J* = 8.4 Hz, ArH), 7.22 (2H, d, *J* = 8.8 Hz, ArH), 7.93 and 9.40 (2H, 2s, 2NH).

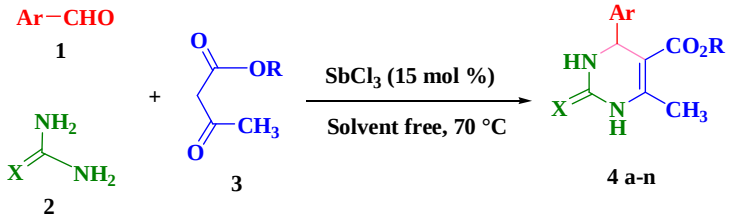
5-Ethoxycarbonyl-6-methyl-4-(4-nitro-phenyl)-3,4-dihydropyrimidin-2(1H)-one (4m). M.p.: 205-207 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 1.10 (3H, t, *J* = 9.6 Hz, $\underline{CH_3}CH_2$), 2.28 (3H, s, CH_3), 3.99 (2H, q, *J* = 9.2 Hz, CH_2O), 5.27 (1H, s, CHN), 7.50-7.53 (2H, m, ArH), 7.23 (2H, d, *J* = 9.2 Hz, ArH), 7.92 and 9.38 (2H, 2s, 2NH).

5-Ethoxycarbonyl-6-methyl-4-(4-methyl-phenyl)-3,4-dihydropyrimidin-2(1H)-one (4n). M.p.: 205-207 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 1.11 (3H, t, *J* = 7.2 Hz, $\underline{CH_3}CH_2$), 2.26 (6H, d, *J* = 9.2 Hz, $2CH_3$), 3.99 (2H, q, *J* = 7.2 Hz, CH_2O), 5.11 (1H, s, CHN), 7.13 (4H, s, ArH), 7.70 and 9.17 (2H, 2s, 2NH).

RESULTS AND DISCUSSION

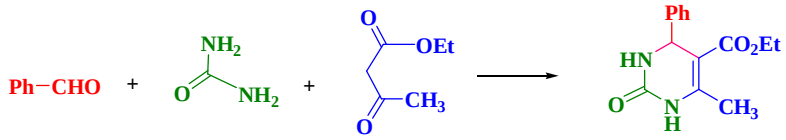
A Lewis acidic catalyst for an efficient and simple methodology to diverse synthesis of 3,4-dihydropyrimidin-2-(1*H*)-one derivatives *via* one-pot three-component condensation Biginelli reaction of aldehydes derivatives (1, 1.0 mmol), urea/thiourea (2, 1.5 mmol) and ethyl/methyl acetoacetate (3, 1.0 mmol) by using of $SbCl_3$ under solvent-free and thermal conditions is described (Scheme 1).

To optimize the reaction conditions, the synthesis of compound 4a (Table 3, entry 1) was used as a model reaction. The effect of different amounts of catalyst on the reaction has been studied in this protocol. No product was detected in the absence of the catalyst even after 8 h (Table 1, entry 1). Good yields were obtained in the presence of catalyst. The best amount of catalyst was 15 mol% (0.034 g) (Table 1, entry 4). The higher amount of catalyst did not increase the yield of



Scheme 1. Synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones derivatives

Table 1. Optimization of the Reaction Condition[a]



Entry	$SbCl_3$ (mol%)	Time (min)	Product	Isolated yields (%)
1	Catalyst free	480	4a	Not product
2	5	45	4a	34
3	10	40	4a	58
4	**15**	**25**	**4a**	**83**
5	20	25	4a	85

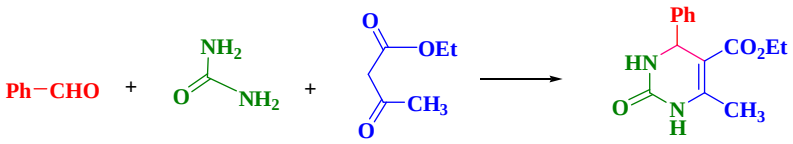
[a]Reaction conditions: benzaldehyde (1.0 mmol), ethyl acetoacetate (1.0 mmol), urea (1.5 mmol) and $SbCl_3$ were heated at 70 °C for an appropriate time.

products (Table 1, entry 5). However, the maximum yield of product was obtained with 0.034 g of catalyst, as indicated in the results summarized in Table 1.

The effect of temperature on the reaction has been also studied. No product was detected at room temperature conditions (Table 2, entry 1). The reaction was investigated by changing temperature from 50-80 °C, and the high yield of product was obtained in 70 °C temperature. The yield of products at different temperatures are reported in Table 2.

To study this procedure, we have synthesized a series of compounds with the type of electron-donating and electron-withdrawing aldehydes derivatives such as Cl, NO_2, OH, OMe, …. substituted banzaldehydes which gave excellent yields. The generality of this three-condensation reaction was studied by using of antimony trichloride (15 mol%) *via* the type of aldehyde derivatives (1.0 mmol), urea or thiourea (1.5 mmol) and ethyl/methyl acetoacetate (1.0 mmol), under solvent-free conditions at 70 °C temperature, as the results shown in Table 3. The proposed mechanistic route for the 3,4-dihydropyrimidin-2-(1*H*)-one synthesis in the presence of $SbCl_3$ is shown in Scheme 2. In this probable mechanism, the $SbCl_3$ catalyzed Biginelli condensation *via* acylimin intermediate A is presented in Scheme 2. The reaction of aldehydes 1 and urea 2 generates an acylimin intermediate A, which further reacts with the activated 1,3-dicarbonyl compound B producing an

Table 2. Effect of Temperature on the Synthesis of **4a**[a]



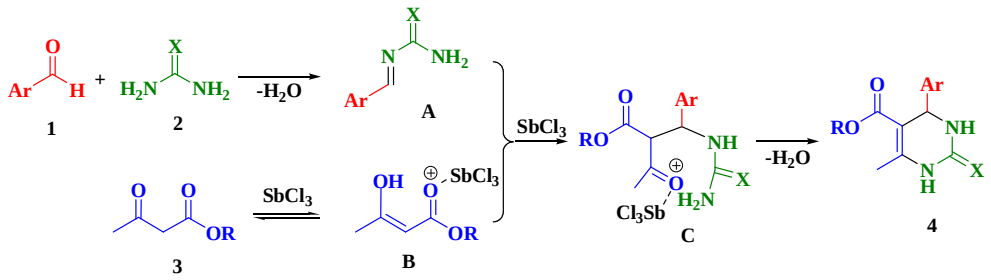
Entry	Temperature (°C)	Time (min)	Product	Isolated yields (%)
1	rt	480	4a	Not product
2	50	60	4a	37
3	60	45	4a	69
4	**70**	**25**	**4a**	**83**
5	80	25	4a	86

[a]Reaction conditions: benzaldehyde (1.0 mmol), ethyl acetoacetate (1.0 mmol), urea (1.5 mmol) and $SbCl_3$ (15 mol%) were heated under various temperatures for an appropriate time.

Table 3. $SbCl_3$ Catalyzed Synthesis of 3,4-Dihydropyrimidin-2-(1*H*)-one Derivatives

Entry	Ar	R	X	Product	Time (min)	Yield (%)[a]	M.p. (°C)	Lit. M.p. (°C)
1	C_6H_5	C_2H_5	O	**4a**	25	83	200-202	200-202[17]
2	C_6H_5	C_2H_5	S	**4b**	35	81	206-208	208-210[17]
3	2-Cl-C_6H_4	CH_3	O	**4c**	40	78	246-248	248-252[17]
4	2-Cl-C_6H_4	C_2H_5	O	**4d**	45	75	220-222	220-223[17]
5	4-OMe-C_6H_4	C_2H_5	O	**4e**	35	81	203-205	202-203[19]
6	4-OMe-C_6H_4	CH_3	O	**4f**	30	83	193-195	190-194[22]
7	4-OMe-C_6H_4	C_2H_5	S	**4g**	45	79	150-152	150-152[17]
8	4-F-C_6H_4	C_2H_5	O	**4h**	20	87	172-174	174-176[21]
9	4-F-C_6H_4	CH_3	S	**4i**	25	85	209-211	208-210[21]
10	3-Cl-C_6H_4	C_2H_5	O	**4j**	45	75	192-194	191-193[17]
11	4-OH-C_6H_4	C_2H_5	O	**4k**	60	72	232-234	230-232[17]
12	4-O_2N-C_6H_4	CH_3	O	**4l**	20	85	215-217	214-216[17]
13	4-O_2N-C_6H_4	C_2H_5	O	**4m**	25	82	205-207	207-209[17]
14	4-Me-C_6H_4	C_2H_5	O	**4n**	35	81	205-207	204-205[18]

[a]Isolated yield.



Scheme 2. Proposed mechanistic route for the synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones

Table 4. Comparing the Catalytic Ability of some Catalysts Reported in the Literature for the Synthesis of 3,4-Dihydropyrimidin-2-(1*H*)-one Derivatives[a]

Entry	Catalyst	Conditions	Time/Yield (%)	Ref.
1	Bakers' yeast	Room temperature	24 h/84	[18]
2	Hydrotalcite	Solvent-free, 80 °C	35 min/84	[19]
3	$[Al(H_2O)_6](BF_4)_3$	MeCN, Reflux	20 h/81	[20]
4	$Cu(BF_4)_2.xH_2O$	Room temperature	30 min/90	[22]
5	[Btto][*p*-TSA]	Solvent-free, 90 °C	30 min/96	[23]
6	Triethylammonium acetate	Solvent-free, 70 °C	45 min/90	[24]
7	*p*-dodecylbenzenesulfonic acid	Solvent-free, 80 °C	3 h/94	[25]
8	$SbCl_3$	Solvent-free, 70 °C	25 min/83	This work

[a]Based on the three-component reaction of benzaldehyde, ethyl acetoacetate and urea.

open-chain ureide C undergoing subsequent cyclization and dehydration to give the major product 4.

Comparing the catalytic ability of some catalysts reported in the literature for the synthesis of 3,4-dihydropyrimidin-2-(1*H*)-one derivatives are shown in Table 4. This study reveals that $SbCl_3$ has shown its extraordinary potential to be an alternative efficient, low-cost and economical catalyst for the Biginelli reaction. In Addition, the use of solvent-free conditions with excellent yields and short reaction times in the reaction with both urea and thiourea are the notable advantages for the present methodology.

CONCLUSIONS

In summary, we described a simple and economical protocol for the synthesis of 3,4-dihydropyrimidin-2-(1*H*)-one derivatives under thermal and solvent-free conditions. Antimony trichloride ($SbCl_3$) has a high efficiency as a Lewis solid acidic catalyst for the multi-component Biginelli synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones derivatives between β-keto esters, aldehyde derivatives and urea/thiourea. The notable advantages for this methodology are low-cost catalyst, highly efficient conditions, high catalytic activity, solvent-free conditions, simple operational and eco- friendly procedures.

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